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Ustekinumab for the treatment of psoriatic arthritis: an update

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Abstract: Psoriatic arthritis occurs in 30% of psoriasis patients, and the treatment can be challenging in some patients. Recently, the US Food and Drug Administration approved ustekinumab, a fully human monoclonal antibody, for the management of psoriatic arthritis. In this article, we review large-scale randomized clinical trials addressing the efficacy and safety profile of ustekinumab for the treatment of psoriatic arthritis.

Keywords: psoriatic arthritis, psoriasis, ustekinumab

Introduction

Psoriatic arthritis (PsA) is an incapacitating seronegative arthritis that occurs in up to 30% of patients with psoriasis.¹⁻³ PsA is more prevalent among patients with relatively severe psoriasis. Risk factors for a more severe course of arthritis include initial presentation at an early age, female sex, polyarticular involvement, genetic predisposition, and radiographic signs of the disease early on.³ The following classification has been outlined by Moll:⁴ mono- and asymmetric oligoarthritis (including the classic involvement of the whole digit referred to as the “sausage” digit), arthritis of the distal interphalangeal joints, rheumatoid arthritis-like presentation, arthritis mutilans, and spondylitis and sacroiliitis.

In recent years, among biologic agents, TNF α inhibitors have been a mainstay for the treatment of PsA.⁵ Although these agents can remarkably improve the clinical manifestations of PsA and prevent radiographic joint damage,^{5,6} a number of patients fail to respond to TNF α inhibitors, experience recurrence, or develop resistance to these therapies. The introduction of ustekinumab and similar drugs was therefore considered an advancement in the management of emergent or refractory PsA. In 2008 and 2009, ustekinumab was approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), respectively, for the treatment of moderate-to-severe plaque psoriasis in adult patients. In September 2013, the EMA and FDA also approved ustekinumab for the treatment of PsA. In this article, we review the pharmacodynamics, pharmacokinetics, efficacy, and safety profile of ustekinumab for the management of PsA.

Pharmacodynamics and pharmacokinetics

Ustekinumab is a fully human immunoglobulin G₁ monoclonal antibody against the shared p40 subunit of IL-12 and IL-23, thereby preventing IL-12 and IL-23 from binding to the receptor chain IL-12R β 1 to trigger downstream signaling pathways.⁷ The pathways

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activated by IL-12 and IL-23 are well established, and are linked to the pathogenesis of psoriasis. It has been demonstrated that dendritic cells and macrophages can overexpress IL-12 and IL-23 cytokines in psoriatic lesions.⁸ IL-12 is a proinflammatory cytokine involved in differentiating naïve T cells into T-helper (Th)-1 cells and producing IFN γ and TNF α .⁹ IL-23 enables the expansion of Th17-positive cells, which produce IL-17 and other cytokines.^{10,11} Studies support the fundamental role of IL-23 and Th-17 in the pathogenesis of psoriasis.^{12,13} In addition, Filer et al noted that variations in the IL-23 receptor and IL-12B single nucleotide polymorphisms are associated with susceptibility to both psoriasis and PsA.¹⁴ Although psoriasis and PsA have been recently shown to have similar susceptibility loci and considerable genetic overlap,¹⁵ it is still not clear that both conditions respond equally well to ustekinumab.

The pharmacokinetic properties of ustekinumab in human patients have been evaluated. Zhu et al reported that the mean values for apparent clearance, apparent volume of distribution, and absorption-rate constant were similar among PsA patients and patients with mild-to-severe psoriasis.¹⁶ Importantly, the patient's body weight and the levels of antibodies against ustekinumab significantly affected the pharmacokinetic properties,¹⁶ although the significance of antiustekinumab antibodies has not yet been determined.¹⁷ Other variables, such as age, sex, disease duration, and baseline Psoriasis Area and Severity Index (PASI) score showed no remarkable effects on the volume of distribution or clearance values.¹⁶ Indeed, in a population-based pharmacokinetic analysis, there were no apparent changes in pharmacokinetic properties among elderly patients.⁷ Also, it has been shown that the clearance of ustekinumab was not changed by concurrent administration of methotrexate, nonsteroidal anti-inflammatory drugs, oral corticosteroids, or prior exposure to anti-TNF α agents in PsA patients.⁷

Efficacy

Multiple clinical trials have demonstrated the beneficial efficacy of ustekinumab in psoriasis patients. Kauffman et al reported that 67% of patients treated with ustekinumab showed a PASI 75 over the course of a 16-week Phase I study.¹⁸ In another Phase I study, compared to no symptom improvement for the placebo group, 76% of patients treated with ustekinumab achieved 75% improvement in PASI score.¹⁹ In a Phase II dose-ranging randomized clinical trial (RCT), PASI 75 was achieved by week 12 with a distinct dose-dependence: 52% of patients treated with a single 45 mg dose, 59% of patients treated with a single

90 mg dose, 67% of patients treated with 45 mg doses every 4 weeks, and 81% of patients treated with 90 mg doses every 4 weeks.²⁰ Over the same time period, only 2% of placebo-treated patients achieved PASI 75. In the phase III PHOENIX (Psoriasis Followed by Long-Term Extension) 1 trial with 766 patients, 67.1% of patients treated with 45 mg ustekinumab and 66.4% of patients treated with 90 mg ustekinumab achieved PASI 75 after 12 weeks, whereas 3.1% of the placebo-treated patients achieved PASI 75.²¹ PHOENIX 2 showed comparable results in 1,230 patients. PASI 75 was achieved in 66.7% of patients receiving ustekinumab 45 mg, 75.7% receiving ustekinumab 90 mg, and 3.7% receiving placebo.²² The Phase III ACCEPT (Active Comparator [CNT01275/Enbrel] Psoriasis Trial) showed PASI 75 in 67.5% of the group treated with 45 mg ustekinumab, 73.8% of the group treated with 90 mg ustekinumab, and 56.8% of the group treated with 50 mg etanercept.²³ Finally, PEARL (Efficacy and Safety of Ustekinumab for the Treatment of Moderate-to-Severe Psoriasis: A Phase III, Randomized, Placebo-Controlled Trial in Taiwanese and Korean Patients) evaluated an Asian population of psoriasis patients, and found PASI 75 in 67.2% of ustekinumab-treated patients, compared to only 5.0% of placebo-treated patients.²⁴

Thus far, there have been no Phase I clinical trials investigating the dose response or safety profile of ustekinumab for treating PsA. Support for conducting later-stage clinical trials for PsA efficacy was based on Phase I evidence for efficacy reported from clinical trials for the treatment of moderate-to-severe plaque psoriasis.^{17,18} One Phase II²⁵ and two Phase III^{26,27} large-scale RCTs investigated the efficacy and safety of ustekinumab in the management of PsA. The results of these trials were published recently, and are summarized in Table 1.

The first study was a randomized, multicenter, double-blind, placebo-controlled, crossover Phase II trial that was published in 2009.²⁵ In this study, 146 patients with active PsA were recruited at multiple clinical sites in Europe and North America, with inclusion criteria consisting of three or more swollen joints, three or more tender joints, and either a C-reactive protein (CRP) level of at least 15 mg/L or a minimum of 45 minutes of daily morning stiffness. Patients were also required to have at least one active skin psoriatic lesion of 2 cm or larger. Patients were randomly assigned to two treatment groups. Patients in the first group received weekly subcutaneous ustekinumab (90 or 63 mg) for 4 weeks, followed by placebo at weeks 12 and 16, and patients in the second group received placebo every week for 4 weeks, followed by ustekinumab (63 mg) at weeks 12 and 16.

Table I A summary of the main outcomes presented in Phase II and III trials comparing ustekinumab to placebo

Outcome measure	Study	Concurrent therapy	Treatment groups				P-values		
			Placebo		Ustekinumab 63 or 90 mg				
ACR 20 response	Gottlieb et al ²⁵	All patients	32/76 (42%)		10/70 (14%)		0.0002		
	McInnes et al ²⁶	All patients		Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined ustekinumab	<0.0001 for all comparisons versus placebo	
				47/206 (22.8%)	87/205 (42.4%)	101/204 (49.5%)	188/409 (46.0%)		
				With MTX treatment	25/96 (26.0%)	43/99 (43.4%)	46/101 (45.5%)		89/200 (44.5%)
				Without MTX treatment	22/110 (20.0%)	44/106 (41.5%)	55/103 (53.4%)		99/209 (47.4%)
	Ritchlin et al ²⁷	All patients		21/104 (20.2%)	45/103 (43.7%)	46/105 (43.8%)	91/208 (43.8%)	<0.001 for all comparisons versus placebo	
				With MTX treatment	14/49 (28.6%)	27/54 (50.0%)	21/52 (40.4%)		48/106 (45.3%)
				Without MTX treatment	7/55 (12.7%)	18/49 (36.7%)	25/53 (47.2%)		43/102 (42.2%)
				Placebo	Ustekinumab 63 or 90 mg				
PASI 75 response	Gottlieb et al ²⁵	All patients	3/55 (5%)		33/63 (52%)		<0.0001		
	McInnes et al ²⁶	All patients		Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined ustekinumab	<0.0001 for all comparisons versus placebo	
				16/146 (11.0%)	83/145 (57.2%)	93/149 (62.4%)	176/294 (59.9%)		
				With MTX treatment	10/66 (15.2%)	32/66 (48.5%)	38/69 (55.1%)		70/135 (51.9%)
				Without MTX treatment	6/80 (7.5%)	51/79 (64.6%)	55/80 (68.8%)		106/159 (66.7%)
	Ritchlin et al ²⁷	All patients		4/80 (5.0%)	41/80 (51.3%)	45/81 (55.6%)	86/161 (53.4%)	<0.001 for all comparisons versus placebo	
				With MTX treatment	3/29 (10.3%)	19/39 (48.7%)	22/39 (56.4%)		41/78 (52.6%)
				Without MTX treatment	1/51 (2.0%)	22/41 (53.7%)	23/42 (54.8%)		45/83 (54.2%)

Abbreviations: ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; MTX, methotrexate.

An American College of Rheumatology (ACR) 20 response (20% or greater improvement in arthritis²⁸) at week 12 was defined as the primary end point of the study.

After 12 weeks, ACR 20 was observed in 42.1% of ustekinumab treated patients versus 14.3% of patients who received placebo. At week 36, 34% of patients in the ustekinumab-treated group, who had not received the drug for 33 weeks, still showed ACR 20. ACR 20 was also observed in 51% (week 24), 45% (week 28), and 42% (week 36) of patients treated with placebo followed by ustekinumab. ACR 50 and ACR 70 were achieved in 25% and 11% of ustekinumab-treated patients, compared to 7% and 0 in the placebo group, respectively. Additionally, the ustekinumab group showed a significantly larger decrease from baseline in the Health

Assessment Questionnaire Disability Index (HAQ-DI) than the placebo group at week 12 (−0.25 [interquartile range −0.50 to 0] versus 0 [interquartile range −0.25 to 0.13], respectively).

Moreover, PASI scores were assessed in patients with psoriatic lesions affecting 3% or more of their body surface area. At week 12, PASI 75 was achieved in 52% of the ustekinumab-treated group and 5% of the placebo-treated group. Among this cohort of patients, Dermatology Life Quality Index (DLQI) data showed a significantly greater median decrease from baseline in ustekinumab-treated patients than in placebo-treated patients at week 12 (−6.0 [interquartile range −14.0 to −3.0] versus 0 [interquartile range −4.0 to 2.0], respectively). This study

demonstrated the superior efficacy of ustekinumab compared to placebo in improving the signs and symptoms of PsA as well as skin psoriatic lesions.

The two Phase III studies for PsA treatment – PSUMMIT (Study of the Safety and Effectiveness of Ustekinumab in Patients with Psoriatic Arthritis) ¹²⁶ and PSUMMIT 2²⁷ – were multicenter, randomized, double-blind, placebo-controlled trials that assessed the efficacy and safety of ustekinumab in large populations of PsA patients.

In PSUMMIT 1, 1,174 patients were screened, and 615 eligible patients with active PsA were randomly assigned to treatment groups. The patient population was from 14 countries in North America, Europe, and the Asia-Pacific region. The patients were included if they had at least five swollen joints, at least five tender joints, CRP ≥ 3 mg/L, and an active or past history of plaque psoriasis. Patients were randomly grouped to receive either subcutaneous ustekinumab 45 mg, subcutaneous ustekinumab 90 mg, or placebo at weeks 0 and 4, and every 12 weeks thereafter. Patients were evaluated at week 16, and those with less than 5% improvement in tender and swollen joint count were switched to another treatment arm: patients receiving placebo entered the ustekinumab 45 mg group, and patients treated with ustekinumab 45 mg entered the ustekinumab 90 mg group. Finally, all patients who remained in the placebo group received ustekinumab 45 mg at weeks 24 and 28, and then every 12 weeks thereafter. The primary end point of the study was defined as ACR 20 at week 24. The secondary end points at week 24 were ACR 50 and ACR 70, PASI 75, 28-joint Disease Activity Score based on CRP (DAS28-CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), HAQ-DI, 36-item Short-Form Health Survey (SF-36), and DLQI scores.

The patients in the ustekinumab 45 mg group and 90 mg group had significantly higher rates of ACR 20 response (42.4% and 49.5%, respectively) than the patients in the placebo group (22.8%) at week 24. The authors also reported significant differences at week 24 for ACR 50. An ACR 50 response was achieved in 24.9% of patients in the ustekinumab 45 mg group, 27.9% of patients in the ustekinumab 90 mg group, and 8.7% of patients in the placebo group ($P < 0.0001$ for all ustekinumab versus placebo comparisons). The same trend was observed for ACR 70: 12.2% of ustekinumab 45 mg patients, 14.2% of ustekinumab 90 mg patients, and 2.4% of placebo patients ($P = 0.0001$ for 45 mg group versus placebo, and $P < 0.0001$ for 90 mg group versus placebo). While only 11.0% of patients in the placebo-treated group had a PASI 75 response, 57.2% and 62.4% of patients in the 45 mg and 90 mg ustekinumab groups achieved a PASI 75

response. Notably, the results were irrespective of concurrent methotrexate therapy. Additionally, ustekinumab appeared to be more efficacious than placebo when DAS28-CRP, BASDAI 20, and quality-of-life measures such as HAQ-DI, SF-36, and DLQI were taken into consideration. PSUMMIT 1 also reported clinically important and statistically significant results regarding the effect of ustekinumab on patients with enthesitis or dactylitis. At week 24, enthesitis was present in 68.6% and 60.8% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 81.0% of patients in the placebo group. Similar results were noted when patients were examined for dactylitis (56.6%, 55.8%, and 76.1%, respectively). At present, TNF α blockers are the only FDA-approved drugs for these conditions. The promising efficacy of ustekinumab on dactylitis and enthesitis in addition to spondyloarthritis may provide a further therapeutic option for these patients.²⁹

Ustekinumab also showed an efficacious effect in placebo-treated patients after switching to ustekinumab. Among 120 patients that began receiving ustekinumab at week 24, ACR 20 scores were achieved in 65.2% by week 52, a comparable result to the other treatment groups. Similarly, PASI 75 response was reached in 67.7% of patients in the placebo group that crossed over at week 24, compared to 68.1% of patients in the ustekinumab 90 mg group ($P > 0.05$). Other outcome measures, such as ACR 50, ACR 70, quality-of-life measures, and skin indices, showed the same trend at week 52. It is important to consider the fact that this trial was not placebo-controlled beyond 24 weeks. Therefore, the results beyond this time point should be interpreted cautiously.

In PSUMMIT 2, 312 patients with PsA were randomly assigned to be treated with 45 mg or 90 mg ustekinumab or a placebo. Patients were randomized using a stratified central randomization method. Similar to PSUMMIT 1, the treatments occurred at weeks 0, 4, and every 12 weeks thereafter. The PsA patients were required to have active PsA for at least 6 months. The eligible patients on other treatments also had a minimum refractory period to other treatments, including disease-modifying antirheumatic drugs, (3 months), non-steroidal anti-inflammatory drugs (4 weeks), etanercept, adalimumab, golimumab, or certolizumab pegol (8 weeks), or infliximab or other TNF antagonists (14 weeks). Concurrent methotrexate therapy was allowed if started more than 3 months before commencement of the trial and if at a stable dose of ≤ 25 mg/week for at least 4 weeks. Patients who had less than 5% improvement in their joint symptoms entered a “blinded early escape” at week 16. This protocol involved patients receiving placebo switching to ustekinumab 45 mg,

those receiving ustekinumab 45 mg switching to ustekinumab 90 mg, and patients receiving ustekinumab 90 mg continuing with blinded 90 mg dosing. Placebo-treated patients who did not start the early escape crossed over to receive ustekinumab 45 mg at week 24 and thereafter. The primary end point of this trial was the same as for PSUMMIT 1, and included ACR 20 at week 24. Other end points included PASI score, DAS28-CRP less than 2.6, DLQI, SF-36, 0.3 or more unit improvement in HAQ-DI, presence of dactylitis, enthesal tenderness or pain using the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score 24, BASDAI, and level of fatigue using the 13-item Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) questionnaire.

The ACR 20 response for PSUMMIT 2 at week 24 was very similar in the 45 mg and the 90 mg ustekinumab groups (43.7% and 43.8%, respectively). Both doses achieved a significantly higher response rate when compared to the placebo group (20.2%, $P < 0.001$ compared to either ustekinumab-treatment groups). The number of patients who achieved DAS28-CRP response was comparable in both of the ustekinumab groups, with a cumulative response of 53.8%, and both were significantly higher than the placebo group, with a 29.8% response. PASI 75 response was achieved in a higher proportion of the ustekinumab-treated than placebo-treated patients at week 24, and all comparisons showed statistically significant efficacy (Table 1), irrespective of the status of methotrexate therapy or body weight. All the quality-of-life measures (HAQ-DI score, FACIT-Fatigue score, DLQI score, and SF-36 score) were significantly improved in both ustekinumab groups versus the placebo group, except the mental component of SF-36, which was comparable between all groups at week 24. Patients with enthesitis and dactylitis responded better to both ustekinumab groups than the placebo group. However, this improvement only reached statistical significance in patients with enthesitis.

Among those patients who received methotrexate, an ACR 20 response was achieved at week 24 in 35.6% of patients in the combined ustekinumab groups versus 14.5% of patients in the placebo group ($P < 0.01$). The PASI 75 response was even more apparent in the combined ustekinumab groups compared to the placebo group among the same subgroup of patients (47.1% versus 2.0%, $P < 0.01$). Among patients who were on TNF α inhibitors, median changes in HAQ-DI scores were significantly more pronounced (-0.13 , interquartile range -0.38 to 0) in the combined ustekinumab groups than the placebo-treatment group (0 , interquartile range -0.13 to 0.13) ($P < 0.05$).

In a recent updated report of PSUMMIT 1 and PSUMMIT 2, Kavanaugh et al showed that both

ustekinumab 45 mg and ustekinumab 90 mg can provide a sustained inhibition of radiographic progression of joint damage, and this effect was significantly higher than the placebo group. The PsA-modified van der Heijde–Sharp score was used to evaluate hand or foot radiographs to monitor the progression of joint involvement. The placebo group had a significantly higher average score (1.0 ± 3.9) at week 24 when compared to the ustekinumab 45 mg (0.4 ± 2.1) and 90 mg groups (0.4 ± 2.4).³⁰

Safety

The safety profile of ustekinumab has been extensively examined for the treatment of psoriasis as well as PsA. The Phase III multicenter PSUMMIT 1, which administered treatment of 45 mg ustekinumab, 90 mg ustekinumab, or placebo for 52 weeks, demonstrated a 42% rate by week 16 and 49.5% by week 24 of at least one adverse event (AE) occurring in the combined ustekinumab-treatment groups.²⁶ The most common AEs of the combined ustekinumab-treatment groups for psoriasis were respiratory tract infections, headaches, arthralgia, and nasopharyngitis. There was a combined 1.7% rate of serious AEs, with consequent discontinuation of treatment in six patients.²⁶

In a randomized clinical study of 146 patients with PsA treated with ustekinumab, the treatment was reasonably well tolerated.²⁵ Patients were administered a 63 mg or 90 mg dose of ustekinumab or a placebo. By 12 weeks of treatment, 61% of the patients in the combined treatment groups and 63% of the patients in the placebo group had one or more AEs, suggesting that ustekinumab was well tolerated compared to placebo. By week 36, the treatment group had 76% of participants with an AE compared to 63% of the patients treated with placebo followed by ustekinumab.²⁵ Similar to ustekinumab treatment for psoriasis, the majority of AEs were upper respiratory tract infections or nasopharyngitis.

In PSUMMIT 1, 615 adult PsA patients were randomized to receive 45 mg/90 mg/placebo treatment and were followed for 2 years.³¹ The placebo-treated patients began 45 mg ustekinumab therapy at week 24. A total of 490 of the participants completed the study, with 5% of the participants discontinuing due to serious AEs. The rates (per 100 patient-years of follow-up) of serious infections, malignancies, and major adverse cardiovascular events were 1.23, 0.38, and 0.66, respectively, in the ustekinumab-treated groups when combined.³¹

In PSUMMIT 2, with 312 patients with PsA, ustekinumab was administered at doses of 45 mg or 90 mg or a placebo, with the placebo group crossing over to 45 mg

ustekinumab at 24 weeks.²⁷ After 16 weeks of treatment, the combined ustekinumab-treatment group had AEs in 61.8% of the patient population compared to 54.8% in the placebo group. These data suggest that ustekinumab is reasonably well tolerated. Even at 24 weeks, the combined ustekinumab group showed 66.4% of the patients having an AE compared to 63.5% for the placebo group.²⁷ The majority of AEs were similar to those found in psoriatic patients, with nasopharyngitis and upper respiratory tract infections as the most common.

A study aggregating the results from a Phase II study,²⁵ PSUMMIT 1, and PSUMMIT 2 results included 1,071 treated patients with PsA.³² The placebo-treated group had 348.07 AEs per 100 patient-years compared to 375.83 for ustekinumab-treated patients in the PsA-specific studies. Furthermore, the placebo group had 12.69 serious AEs compared to 5.75 for the ustekinumab-treated group per 100 patient-years. Results from psoriasis studies with PsA patient subgroups reported similar levels of AEs of 476.42 for the placebo and 481.31 for the ustekinumab-treated groups (events per 100 patient-years).³²

Aggregated data from a Phase II study,²⁰ PHOENIX 1, PHOENIX 2, and ACCEPT included 3,117 patients totaling 8,998 patient years of follow-up and compared the safety of ustekinumab 45 mg or 90 mg treatment in psoriatic patients to the PsA subgroup.³³ Of the 858 patients with PsA totaling 2,490 years of patient follow-up, there were 249.40 AEs per 100 patient-years compared to 232.59 AEs per 100 patient-years for the overall population. Among the AEs, the rate of major adverse cardiovascular events and serious infections for the PsA group was 0.56/100 patient-years and 1.53/100 patient-years compared to 0.44/100 patient-years and 1.10/100 patient-years in the overall population.³³ Therefore, ustekinumab treatment for PsA appears to have comparable results to the overall treated psoriasis population.

There has been extensive research on the safety profile of ustekinumab for the treatment of psoriasis and PsA, and it appears that long-term treatment with ustekinumab does not alter the risks associated with its use. Furthermore, there are no dose-dependent risks associated with ustekinumab use. The safety of ustekinumab is comparable to other approved drugs for the treatment of psoriasis and PsA.

Conclusion

The current literature supports the efficacy and safety of ustekinumab in the treatment of PsA. The results from Phase III trials suggest that ustekinumab is also useful

for treating enthesitis, dactylitis, and spondyloarthritis. Furthermore, data from the PSUMMIT trials suggest that the onset of action is slower with ustekinumab than TNF α inhibitors, although a similar efficacy rate can be achieved by 52 weeks. Future trials comparing these two classes of drugs are essential to further elucidate their relative efficacy.²⁹

Disclosure

The authors report no conflicts of interest in this work.

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